UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/852,058 | 05/09/2001 | Philip Morrison Giffard | DIAT:002 | 3768 |

7590 10/08/2002

Robert M. O'Keefe
O'KEEFE, EGAN & PETERMAN
Building C, Suite 200
1101 Capital of Texas Highway South
Austin, TX 78746

| EXAMINER | |
|---|---|
| GUNTER, DAVID R | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1634 | 13 |

DATE MAILED: 10/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/852,058 | GIFFARD ET AL. | |
| | Examiner | Art Unit | |
| | David Gunter | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 23-27* is/are rejected.

7)☒ Claim(s) *21 and 22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. The examiner acknowledges the applicants claim to priority for the instant application as a continuation of provisional application number 60/202,797 filed May 9,2000.

### *Claim Objections*

2. Claims 21 and 22 are objected to under 37 CFR 1.75(c) as being in the improper form for a multiple dependent claim. Claim 21 is a multiple dependent claim that depends from Claim 20, which is also a multiple dependent claim. Claim 22 depends from Claim 21, and is therefore also improperly multiply dependent. See MPEP § 608.01(n). Accordingly, the claims 21 and 22 are not been further treated on the merits.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-3, 5-19, 23, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. The claims are generally narrative and indefinite, failing to conform to current U.S. practice. The claims must be re-written so that the method steps are set apart as separate sub-paragraphs which are to be designated by sequential letters in parenthesis at the beginning of each sub-paragraph.

b. Regarding Claims 1-3, 5-9, 12-19, 23, and 27, the claim is indefinite because the phrase "capable of" is unclear. "Capable of" is not an active method step, and may be interpreted to recite either a property of the antecedent substance ("reporter molecule" in Claim 1, "primer" in Claim 2, etc.) or a potential method of using the antecedent substance. The claim should be amended to clarify whether the phrase "capable of" is meant to denote a property or a method step. For example, the phrase "reporter molecule capable of providing an identifiable signal" (Claim 1) should be replaced with "reporter molecule that provides an identifiable signal."

c. Regarding Claims 8-11 and 15-16, the terms "high Tm" and "low Tm" are relative terms which render the claim indefinite. The terms "high Tm" and "low Tm" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

d. Regarding Claims 8, 9, 15, and 16, primers or sets of primers are referred to as being "active" or "inactive." This terminology is unclear because primers are not generally considered to have inherent biological activity. For the purpose of examination, a recitation of primers being "active" will be interpreted to mean that annealing of primers to target nucleic acids will be carried out under conditions that favor hybridization of this particular primer or pair of primers to its target. Similarly, a recitation that primers are "inactive" will be interpreted to mean that annealing of primers to target nucleic acids will be carried out under conditions that do not favor hybridization

of this particular primer or pair of primers to its target. However, the claim must be amended to clarify the meaning of "active" and "inactive" primers.

e. Regarding Claims 8, 9, 15, and 16, the phrase "said second amplification" lacks antecedent basis in the Claims because there is no prior recitation of a second amplification of the target DNA.

f. Regarding Claim 14, it appears that in the phrase "the nucleotide sequence ... differs from said target nucleotide sequence but at least one nucleotide mis-match," the word "but" should be replaced with "by."

### *Claim Rejections - 35 USC § 102*

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Schena, et al., Science 270:467-470. 1995 (hereinafter referred to as "Schena"). Claims 12-14 recite a solid support comprising an array of immobilized primers wherein each of the primers may comprise the identical nucleotide sequence or one or more may differ from each other by at least one nucleotide. The remainder of the claim recites a potential use for the solid support, which does not further define the support. Therefore, the portion of the claim reciting a potential use of the solid support has not been considered in the evaluation of the claims because the method of using the support does not define the support, and because the support has a plurality of other potential uses including the identification of DNA-binding proteins. Schena discloses DNA molecules that are immobilized onto glass slides (page 467, right column).

5. Claims 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Fisher et al., Analytical Biochemistry 251:280-287. 1997 (hereinafter referred to as "Fisher"). Claims 15 and 16 recite a nucleic acid molecule anchored to a solid support via hybridization of said nucleic acid to a primer anchored to the solid support. The remainder of the claim recites a potential use of the nucleic acid, which does not further define the nucleic acid. Therefore, the portion of the claim reciting a potential use of the nucleic acid has not been considered in the evaluation of the claims because the method of using the nucleic acid does not define the nucleic acid, and because the nucleic acid has a plurality of other potential uses including the identification of DNA-binding proteins. Fisher discloses nucleic acid molecules that are anchored to a solid support via hybridization of the nucleic acid to a primer anchored to a solid support (page 281, table 1).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-7 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber, U.S. Patent Number 5,834,181, filed September 13, 1996, issued November 10, 1998 (hereinafter referred to as "Shuber"), in view of Fisher. The claims of the instant application recite a method for detection of a nucleic acid molecule having a particular sequence after the nucleic acid has been immobilized to a solid support via hybridization to a primer anchored to the solid support. The method comprises contacting the immobilized nucleic acid with at least two nucleic acid primers, one of which is complementary to the nucleic acid and one of which differs from the target nucleotide by at least one nucleotide. At least one of the primers is labeled with a reporter molecule that provides an identifiable signal, and the detection of the presence of the signal is indicative of which primer has hybridized to the target sequence.

Shuber discloses an identical method for the detection of sequence variations in nucleic acid molecules immobilized to a solid support comprising contacting the immobilized nucleic acid with multiple nucleic acid primers which are complementary to the immobilized nucleic acid or which contain one or more substitutions. The nucleic acid primers "can be identified by any method well-known in the art, such as, for example sequencing, direct labeling, indirect labeling, and labeling with a unique length marker" (Column 2, lines 28-44). Following hybridization of the primers to the immobilized nucleic acid, detection of the labels present on

the primers allows determination of the sequence and identity of the immobilized nucleic acid molecule.

Shuber does not specifically teach the manner in which the target nucleic acid is immobilized. Shuber states that it "will be understood by a skilled practitioner that the method by which the target nucleic acid is bound to the [substrate] will depend on the particular [substrate] used," (Column 6, lines 50-52) and discloses many potential methods of immobilizing nucleic acids including affinity-dependent mechanisms such as antibodies or biotin / strepavadin. At the time the application was filed, those of skill in the art routinely practiced immobilization of target nucleic acids via hybridization to anchored nucleic acid probes. Fisher, for example, teaches numerous methods of immobilizing nucleic acids to substrates including the use of anchored nucleic acid probes to hybridize to the target nucleic acid (page 281, table 1). Fisher teaches that "the capture of a nucleic acid sequence by allele-specific oligonucleotide probes would provide the most specific and accurate" means of immobilizing a desired nucleic acid. It would have been obvious to one of ordinary skill in the art at the time the application was filed to adapt the method of Shuber to include immobilization of the target nucleotide by hybridization to an immobilized primer, as taught by Fisher, in order to allow the capture of the target nucleic acid in a sequence-specific manner.

a. Regarding Claim 2, the method of Claim 1 is rejected as unpatentable over Shuber in view of Fisher as described above. Shuber discloses the embodiment in which that identification of the primers that hybridize to the target nucleic acid "identifies the nucleic acid sequence or one or more genetic alterations" (Column 2, lines 39-40). In

order for the primers to correctly identify genetic alterations in a specified gene, the must inherently be allele-specific.

Shuber further discloses the embodiment in which the hybridized nucleic acid primers "may be amplified to facilitate detection and identification" and that "examples of amplification methods include polymerase chain reaction" (Column 2, lines 49-53). In order for the nucleic acid primers to be amplified by polymerase chain reaction, it is inherent that the primers are extended from their 3' terminus, and that the resulting amplification produce would be complementary to the strand to which the primer has hybridized.

b. Regarding Claim 3, Claim 3 recites all of the limitations of Claims 1 and 2 without adding any further limitations. Therefore, Claim 3 is rejected as being unpatentable over Shuber in view of Fisher for the reasons described above for Claims 1 and 2.

c. Regarding Claim 4, the method of Claim 1 is rejected as unpatentable over Shuber in view of Fisher as described above. Shuber discloses the embodiment in which the target nucleic acid is amplified to facilitate detection and identification (Column 2, lines 49-51).

d. Claim 5 recites all of the limitations of Claims 3 and 4 without adding any further limitations. Therefore, Claim 5 is rejected as being unpatentable over Shuber in view of Fisher for the reasons described above for Claims 3 and 4.

e. Claim 6 recites all of the limitations of Claims 5 and 2 without adding any further limitations. Therefore, Claim 6 is rejected as being unpatentable over Shuber in view of Fisher for the reasons described for Claims 5 and 2.

f. Claim 7 recites all of the limitations of Claims 1, 2, and 4 without adding any further limitations. Therefore, Claim 7 is rejected as being unpatentable over Shuber in view of Fisher for the reasons described for Claims 1, 2, and 4.

g. Claim 17 recites a slightly different preamble from that of Claim 1, but recites identical method steps. Because the method steps of Claims 1 and 17 are identical, Claim 17 is rejected as being unpatentable over Shuber in view of Fisher for the reasons described above for Claim 1.

h. Claims 18 and 19 recite all of the limitations of Claims 17 and 2 without adding any further limitations. Therefore, Claims 18 and 19 are rejected as being unpatentable over Shuber in view of Fisher for the reasons described above for Claims 17 and 2.

7. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber in view of Tang, et al., Journal of Clinical Microbiology 35(6):1597-1599. 1997 (hereinafter referred to as "Tang"). The claims of the instant application recite a method for detection of a nucleic acid molecule having a particular sequence after the nucleic acid has been immobilized to a solid support via hybridization to a primer anchored to the solid support. The method comprises contacting the immobilized nucleic acid with at least two nucleic acid primers, one of which is complementary to the nucleic acid and one of which differs from the target nucleotide by at least one nucleotide. At least one of the primers is labeled with a reporter molecule that

provides an identifiable signal, and the detection of the presence of the signal is indicative of which primer has hybridized to the target sequence.

Shuber discloses an identical method for the detection of sequence variations in nucleic acid molecules immobilized to a solid support comprising contacting the immobilized nucleic acid with multiple nucleic acid primers which are complementary to the immobilized nucleic acid or contain one or more substitutions. The nucleic acid primers "can be identified by any method well-known in the art, such as, for example sequencing, direct labeling, indirect labeling, and labeling with a unique length marker" (Column 2, lines 28-44). Following hybridization of the primers to the immobilized nucleic acid, detection of the labels present on the primers allows identification of the sequence and identity of the immobilized nucleic acid molecule.

Shuber does not specifically teach the manner in which the target nucleic acid is immobilized. Shuber states that it "will be understood by a skilled practicioner that the method by which the target nucleic acid is bound to the [substrate] will depend on the particular [substrate] used," (Column 6, lines 50-52) and discloses many potential methods of immobilizing nucleic acids including affinity-dependent mechanisms such as antibodies or biotin / strepavadin. At the time the application was filed, those of skill in the art routinely practiced immobilization of target nucleic acids via hybridization to anchored nucleic acid probes. Fisher, for example, teaches numerous methods of immobilizing nucleic acids to substrates including the use of immobilized oligonucleotides to hybridize to the target nucleic acid (page 281, table 1). Fisher teaches that "the capture of a nucleic acid sequence by allele-specific oligonucleotide probes would provide the most specific and accurate" means of immobilizing a desired nucleic acid.

Shuber discloses the embodiment in which that identification of the primers that hybridize to the target nucleic acid "identifies the nucleic acid sequence or one or more genetic alterations" (Column 2, lines 39-40). In order for the primers to correctly identify genetic alterations in a specified gene, the must inherently be allele-specific.

Shuber further discloses the embodiment in which the hybridized nucleic acid primers "may be amplified to facilitate detection and identification" and that "examples of amplification methods include polymerase chain reaction" (Column 2, lines 49-53). In order for the nucleic acid primers to be amplified by polymerase chain reaction, it is inherent that the primers are extended from their 3' terminus, and that the resulting amplification produce would be complementary to the strand to which the primer has hybridized.

Claims 8 and 9 recite the further limitation that the primer used for the first amplification (prior to immobilization of the target nucleic acid) have a higher melting point than those used for the second amplification (after immobilization of the target and hybridization of the labeled nucleic acid primers) such that the primers used for the second amplification are not able to hybridize to the target nucleic acid during the first amplification. Shuber discloses the embodiment in which the target nucleic acid is amplified prior to immobilization and again after hybridization to the labeled nucleic acid primers (Column 2, lines 39-40). Shuber does not specifically teach that the primers necessary for the first and second amplification are all present during the first amplification.

The practice of single-tube nested PCR was routinely practiced by those of skill in the art at the time the application was filed. Nested PCR method allows a target nucleic acid to be amplified twice with two separate sets of primers and allows a much greater degree of

amplification than a single PCR amplification reaction. Single-tube nested PCR is carried out by adding the target nucleic acid, both sets of primers, an appropriate polymerase, and other necessary components to a tube and carrying out both amplification reactions sequentially without the necessity of opening the tube and adding primers or reagents between amplifications. Tang teaches a method in which the two pairs of primers have substantially different melting points so that the conditions present during the first amplification do not favor hybridization of the second set of primers to the target oligonucleotide. The first amplification reaction is run to completion so that all of the first pair of primers are consumed and thus are not available during the second amplification (page 1597, left column, last paragraph through the second paragraph of the right column). It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the method of Shuber to include primer pairs with substantially different melting temperatures are taught by Tang to allow two rounds of PCR amplification to take place while minimizing the risk of contamination associated with handling the reaction mixture between amplifications.

8. Claims 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber in view of Tang in further view of Balaguer, et al. Molecular and Cellular Probes 7:155-159. 1993 (hereinafter referred to as "Balaguer"). Claims 8 and 9 are rejected as unpatentable over Shuber in view of Tang as described above. Claims 10 and 11 recite the additional limitations to Claims 8 and 9 that the immobilized primer has a high (Claim 10) or low (Claim 11) melting temperature. As described above in paragraph 3b, under the section label "Claim Rejections - 35 USC § 112", the terms "high Tm" and "low Tm" are not defined by the claim, the specification

does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Neither Shuber nor Tang disclose alteration of the Tm of the immobilized primer. However, Balaguer teaches that the affinity of an immobilized primer for a target nucleic acid can be increased by increasing the length of the primer (page 158, table 2) or decreased by increasing the number of mis-matches between the primer and the target nucleic acid (page 157, figure 1). It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the length and sequence of the immobilized primer in order to establish a melting point that provides an appropriate degree of sequence specificity between the primer and the target oligonucleotide without interfering in subsequent amplification of the target or liberation of the target from the primer. This melting point would be established as being either "high" or "low" relative to the melting points of the other primers used in the method based on the design of the experiment and the intended results of the method.

9. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber in view of Plassart and Fontaine, Biomedicine and Pharmacotherapy 48:191-197. 1994 (hereinafter referred to as "Plassart"). Claims 17-19 are rejected as being anticipated by Shuber as described above in paragraphs 4(g) and 4(h). Claim 20 recites the further limitation that the nucleotide repeat number polymorphism to be detected by the method of Claims 17-19 is microsatellite DNA. Shuber does not specifically teach the detection of microsatellite DNA.

Plassart teaches that "widely distributed throughout the human genome" and "have been found in the genes causing six different neurological disorders" including Huntington's Disease

(page 191, left column, first paragraph). It would have been obvious to one of ordinary skill in the art at the time the application was filed to apply the method of Shuber to the study of microsatellite DNA for the purpose of detecting genetic changes associated with Huntington's Disease as a means of identifying those at risk for the disease prior to the development of disease symptoms.

10. Claim 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schena in view of Plassart. Claim 23 recites a method in which a target nucleic acid molecule is interrogated by a pair of primers immobilized in separate reaction vessels for separate spot arrays. One primer is capable of priming a particular nucleotide length polymorphism, but the other is not. At least one primer is labeled with a reporter molecule that provides an identifiable signal indicative of the presence or absence of the nucleotide length polymorphism. Claims 24-26 recite the additional limitations that the nucleotide repeat number polymorphism is microsatellite DNA (Claim 24), and that the method is intended to detect a neurodegenerative disease (Claim 25), specifically Huntington's disease (Claim 26).

Schena discloses a method in which a target nucleic acid molecule is interrogated by a plurality of primers immobilized on specific regions of a glass slide. Each of the primers has a unique sequence, and hybridization is carried out at high stringency such that each primer binds specifically to a defined nucleotide sequence. Binding of the target nucleic acid to its corresponding primer produces an identifiable signal that indicates the presence or absence of the target nucleic acid (page 467, right column, second paragraph through page 468, center column). Schena discloses that the label is present on the target nucleic acid and not the primer, but the

examiner notes that the method was routinely practiced at the time the application was filed with the label either attached to the target nucleic acid or to the primer.

Schena does not specifically teach that the DNA to be analyzed by this method is microsatellite DNA, that the method is intended to detect neurodegenerative disease, or that the method is intended to detect Huntington's disease. However, Plassart teaches that "widely distributed throughout the human genome" and "have been found in the genes causing six different neurological disorders" including Huntington's Disease (page 191, left column, first paragraph). It would have been obvious to one of ordinary skill in the art at the time the application was filed to apply the method of Shuber to the study of microsatellite DNA for the purpose of detecting genetic changes associated with Huntington's Disease as a means of identifying those at risk for the disease prior to the development of disease symptoms.

11. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shuber in view of Fisher in further view of Schena. Claim 27 recites a method in which a target nucleic acid molecule is quantified following immobilization of the target nucleic acid to a solid support via hybridization to a primer anchored to the solid support. The immobilized target nucleic acid is brought into contact with at least two primers, at least one of which is complementary to the target nucleic acid and at least one of which contains at least one mismatch. At least one of the primers is labeled with a reporter molecule that provides an identifiable signal. The target nucleic acid is amplified, and the amount of the target nucleic acid present is determined from the ratio of incorporation of the complementary and mismatched primers into the amplified DNA.

Shuber discloses a method for the detection of sequence variations in nucleic acid molecules immobilized to a solid support comprising contacting the immobilized nucleic acid to multiple nucleic acid primers that are complementary to the immobilized nucleic acid or contain one or more substitutions. The nucleic acid primers "can be identified by any method well-known in the art, such as, for example sequencing, direct labeling, indirect labeling, and labeling with a unique length marker" (Column 2, lines 28-44). Following hybridization of the primers to the immobilized nucleic acid, detection of the labels present on the primers allows identification of the sequence and identity of the immobilized nucleic acid molecule. Shuber further discloses the embodiment in which the hybridized nucleic acid primers "may be amplified to facilitate detection and identification" and that "examples of amplification methods include polymerase chain reaction" (Column 2, lines 49-53).

Shuber does not specifically teach the manner in which the target nucleic acid is immobilized. Shuber states that it "will be understood by a skilled practicioner that the method by which the target nucleic acid is bound to the [substrate] will depend on the particular [substrate] used," (Column 6, lines 50-52) and discloses many potential methods of immobilizing nucleic acids including affinity-depending mechanisms such as antibodies or biotin / strepavadin. At the time the application was filed, those of skill in the art routinely practiced the immobilization of a target nucleic acid via hybridization to anchored nucleic acid probes. Fisher, for example, teaches numerous methods of immobilizing nucleic acids to substrates including the use of immobilized oligonucleotides to hybridize to the target nucleic acid (page 281, table 1). Fisher teaches that "the capture of a nucleic acid sequence by allele-specific oligonucleotide probes would provide the most specific and accurate" means of immobilizing a desired nucleic

acid. It would have been obvious to one of ordinary skill in the art at the time the application was filed to adapt the method of Shuber to include immobilization of the target nucleotide by hybridization to an immobilized primer, as taught by Fisher, in order to allow the capture of the target nucleic acid in a sequence-specific manner.

Shuber does not specifically teach that the amplification of the immobilized DNA is performed in a manner than allows determination of the amount of target DNA present in the sample. However, the examiner notes that quantitative and semi-quantitative PCR were routinely practiced at the time the application was filed, as was amplification of nucleic acids immobilized to solid supports. It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the method of Shuber to incorporate quantitative amplification of the target nucleic acid to allow both detection of the target nucleic acid and measurement of its level of expression to better characterize the nucleic acid.

***Conclusion***

**10. No claims are allowed.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David R. Gunter whose telephone number is (703) 308-1701. The examiner can normally be reached on 9:00 - 5:00 M - F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 746-9212 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0198.

David R. Gunter, DVM, PhD
September 30, 2002

STEPHANIE W. ZITOMER
PRIMARY EXAMINER